Memoranda

A REVISED SYSTEM OF NOMENCLATURE FOR INFLUENZA VIRUSES*

The present system of classification of influenza viruses was developed by WHO Expert Committees meeting in 1953 and 1959, and was based on the ribonucleoprotein and haemagglutinin antigens. Since then, another antigen, neuraminidase, has been identified and it has been found that the haemagglutinin and the neuraminidase undergo independent antigenic variation. It is therefore necessary that the system of classification should describe all three antigens. Furthermore, it is now known that both the haemagglutinin and neuraminidase antigens of influenza A viruses of human origin may be similar to, or identical with, those of strains from non-human hosts, and it is necessary that this antigenic relationship should be indicated. For influenza A viruses, therefore, a new system retaining as much as possible of the old system but also including the new information has been developed. It is the intention of WHO that the new system should be brought into use on 1 January 1972.

The WHO Expert Committee on Influenza (1953) recommended that influenza virus strains should be classified into types A, B, and C on the basis of their ribonucleoprotein antigens. It was also recommended that they should be designated according to a uniform code. In strain A/England/1/53, for example, *A* refers to the type, *England* to the place of origin, *1* to the strain serial number, and *53* to the year of isolation. The WHO Expert Committee on Respiratory Virus Diseases (1959) emphasized the importance of a uniform coding system and made provisions for indicating influenza virus subtypes, e.g., A_2/Singapore/1/57, the use of which was considered to be optional. The nomenclature of influenza A viruses of animals followed a similar pattern with the type-specific designation and the species of origin being shown. A subtype designation was often included, e.g., A/equine-2/Miami/1/63, but this was inconsistently applied for viruses from other host species.

It is now well established that the surface of the influenza virus contains an additional virus-coded antigen, the neuraminidase, that is morphologically and immunologically distinct from the haemagglutinin. The haemagglutinin and neuraminidase are known to undergo independent antigenic variation. Therefore, an adequate description of influenza viruses requires that both these antigens be taken into account.

The system recommended in 1953 implied that the antigens of the influenza viruses were unique for strains isolated from a single animal species. In fact, haemagglutinin and neuraminidase antigens related to those of certain human influenza A viruses have been identified among strains isolated from non-human hosts. Viruses antigenically identical to the pandemic virus of 1968 were later isolated also from swine and other mammals. There was no provision in the framework of the 1953 system of nomenclature for the expression of such relationships which may be important in the epidemiology of influenza. The system seriously limited the distribution of information on the antigenic characteristics of influenza virus isolates. The ability to measure and describe fully antigenic changes of the envelope proteins is essential to our understanding of problems of immunity.

The system of nomenclature proposed herein retains as much as possible of the 1953 system, but includes modifications that will permit a more comprehensive description of the virus to be given. The system consists of two parts—namely, a strain designation, and a description of the haemagglutinin and neuraminidase antigens. The strain designation for types A, B, and C contains the following information:

(1) a description of the antigenic type of ribonucleoprotein (A, B, or C);

(2) the host of origin; this is not indicated for strains isolated from man but is indicated for all

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strains isolated from non-human hosts, e.g., swine, horse (equine), duck, chicken, turkey, quail, tern, etc.;

(3) geographical origin;

(4) strain number;

(5) year of isolation.

For influenza A viruses the antigenic description follows the strain designation and includes, in parentheses, the following information.

(1) An index describing the antigenic character of the haemagglutinin subtype. Some examples are:

human	H0, H1, H2, H3
equine	Heq1, Heq2
swine	Hsw1
avian	Hav1, etc.

(2) An index describing the antigenic character of the neuraminidase subtype; for example:

human	N1, N2
equine	Neq1, Neq2
avian	Nav1.

The host designation for the H and N (e.g., H*eq*1, N*av*1) antigens refer to the source of the virus where the antigen was first characterized. It does not imply the existence of phylogenetic or evolutionary relationship between viruses containing a common H or N designation. Such designations are intended to indicate the possession of a common subtype of haemagglutinin or neuraminidase antigen but it is implicit that a given H or N subtype will encompass strains showing a considerable degree of antigenic variation within the subtype.

A full designation of a given isolate would be expressed as shown in the following examples:

(1) A/Hong Kong/1/68 (H3N2);

(2) A/turkey/Wisconsin/1/66 (Hav5N2);

(3) A/swine/Taiwan/1/70 (H3N2).

The strain designation describes the origin of the virus and is essentially the same as in the previous system but omits the subtype designation. The second part of the designation given in parentheses describes the antigenic composition (H and N). Thus in the examples above, the descriptions indicate that the influenza virus isolated from turkeys in Wisconsin contains neuraminidase antigenically related to that of the human Hong Kong/68 isolate and an unrelated haemagglutinin. It also indicates that the virus isolated from swine in Taiwan contains both haemagglutinin and neuraminidase antigens related to those of the human Hong Kong/68 isolate. This system eliminates one of the disadvantages of the previous system of nomenclature whereby two antigenically identical viruses might have quite different designations, e.g., A_2/Hong Kong/1/68 and A/Swine/Taiwan/1/70.

The use of H and N antigen subtype descriptions may be criticized on the grounds that it adds to the already complex method of strain designation. However, in any publication a full description of the strain is usually required only once; thereafter, an abbreviated version may be used. The strain, A/Hong Kong/8/68 (H3N2), for example, once designated, may be later referred to as A/HK/68.

There is no provision for describing H and N subtypes of influenza B and C viruses. The existence of antigenic variation among their strains is known but the information is inadequate to enable a division into subtypes to be made. The description of these viruses is therefore limited to strain designation, e.g., B/England/5/66, C/Paris/1/67.

RECOMBINANT VIRUSES

Recombinant influenza viruses have become widely used in laboratory studies, and a number of different systems have been employed to describe them. To avoid confusion, a standardized system of nomenclature is suggested.

Genetically stable recombinants of influenza A viruses may be produced that contain the haemagglutinin derived from one parent and the neuraminidase from the other (antigenic hybrids). Consequently, the antigenic composition of a recombinant virus containing the haemagglutinin antigen from A/BEL/42 (H0N1) and the neuraminidase from A/Singapore/1/57 (H2N2) would be: A/BEL/42 (H0)–A Singapore/1/57 (N2).

For tabular material or for reference in the test of publications this description may be abbreviated to A/BEL(H0)–Sing(N2).

REFERENCE STRAINS

The appropriate reference strains for each antigen subtype are listed in Tables 1–6.

METHODS OF ANTIGENIC ANALYSIS

1. *The ribonucleoprotein antigen*

The division of influenza virus isolates into types A, B, and C has frequently been based on comple-

Table 1. Antigenic subtypes of haemagglutinin and neuraminidase of influenza A viruses of human origin

H subtype	Reference strain	N subtype	Reference strain
H0	A/PR/8/34 (H0N1) A/Weiss/43 (H0N1)	N1	A/PR/8/34 (H0N1) A/FM/1/47 (H1N1)
H1	A/FM/1/47 (H1N1) A/England/1/51 (H1N1) A/Denver/1/57 (H1N1)		
H2	A/Singapore/1/57 (H2N2) A/England/12/64 (H2N2) A/Tokyo/3/67 (H2N2)	N2	A/Singapore/1/57 (H2N2) A/Hong Kong/1/68 (H3N2)
H3	A/Hong Kong/1/68 (H3N2)		

Table 2. Antigenic subtypes of haemagglutinin and neuraminidase of influenza viruses of swine origin *

H subtype	Reference strain	N subtype	Reference strain
Hsw1	A/swine/Wisconsin/15/30 (Hsw1N1)	N1	A/swine/Wisconsin/15/30 (Hsw1N1) A/PR/8/34/(H0N1)

* With the exception of A/swine/Taiwan/70 (H3N2), the haemagglutinins of influenza isolates from swine show limited degrees of antigenic variation and are regarded as belonging to a single antigenic subtype (Meier-Ewert, Gibbs & Dimmock, 1970; Pereira, 1969; Schild et al., unpublished data). The neuraminidases of swine influenza isolates are antigenically related (Paniker, 1968; Schild et al., unpublished data) and are regarded as belonging to the human N1 subtype.

Table 3. Antigenic subtypes of haemagglutinin and neuraminidase of influenza A viruses of equine origin

H subtype	Reference strain	N subtype	Reference strain
Heq1	A/equine/Prague/1/56 (Heq1Neq1)	Neq1	A/equine/Prague/1/56 (Heq1Neq1)
Heq2	A/equine/Miami/1/63 (Heq2Neq2)	Neq2	A/equine/Miami/1/63 (Heq2Neq2)

ment-fixation tests performed with guinea pig antisera containing antibody to the "soluble" (i.e., ribonucleoprotein) antigen of the influenza virus (WHO Expert Committee on Respiratory Virus Diseases, 1959). The typing of sera prepared from extracts of virus-infected chorioallantoic membranes appears to be generally acceptable although the antisera cannot be regarded as monospecific and may contain antibody to other virus-coded, or host-cell, antigens. Technical advances in the recognition

Table 4. Antigenic subtypes of haemagglutinin and neuraminidase of avian influenza A viruses

H subtype	Reference strain	N subtype	Reference strain
Hav1	A/FPV/Dutch/27 (Hav1Neq1) [a]	Nav1	A/duck/England/56 (Hav3Nav1)
Hav2	A/chicken/Germany " N "/49 (Hav2N1)	Nav2	A/tern/S. Africa/61 (Hav5Nav2)
Hav3	A/duck/England/56 (Hav3Nav1)	Nav3	A/turkey/England/63 (Hav1Nav3)
Hav4	A/duck/Czech/56 (Hav4Nav1)	Nav4	A/turkey/Ontario/6118/68 (Hav8Nav4)
Hav5	A/tern/S. Africa/61 (Hav5Nav2)		
Hav6	A/turkey/Mass./65 (Hav6N2)		
Hav7	A/duck/Ukraine/1/63 (Hav7Neq2)		
Hav8	A/turkey/Ontario/6118/68 (Hav8Nav4)		

[a] Designation of H subtypes follows the scheme previously suggested (Pereira, Rinaldi & Nardelli, 1967; Paniker, 1968; Meier-Ewert, Gibbs & Dimmock, 1970). Some of the avian influenza viruses have been shown to contain neuraminidase antigenically closely related to that of human neuraminidase N1 (Schild, Pereira & Schettler, 1969; Tumova & Schild, unpublished data), to N2 (Pereira, Tumova & Webster, 1967; Webster & Pereira, 1968; Schild & Newman, 1969), and to equine neuraminidase Neq1 and Neq2 (Webster & Pereira, 1968; Tumova & Schild, unpublished data), and they have been assigned to the appropriate subtypes.

and isolation of the ribonucleoprotein antigen now make possible the preparation of monospecific antisera. In addition, identification of influenza A and B viruses may be achieved by the use of immunoprecipitin tests in gels (Beard, 1970; Schild & Pereira, 1969). The complement-fixation and immunoprecipitin tests may be considered as optional alternatives.

Haemagglutinin and neuraminidase antigens

The revised system of influenza nomenclature requires that the envelope antigens, the haem-

Table 5. Antigenic characteristics of reference influenza A viruses *

Neuraminidase subtypes	Haemagglutinin subtypes														
	H0	H1	H2	H3	Hsw1	Heq1	Heq2	Hav1	Hav2	Hav3	Hav4	Hav5	Hav6	Hav7	Hav8
N1	1	2			5										
N2			3	4									14		
Neq1						6		8	10						
Neq2							7							15	
Nav1										11	12				
Nav2												13			
Nav3								9							
Nav4															16

* Previous designations:

1 = AO/PR/8/34
2 = A1/FM/1/47
3 = A2/Singapore/1/57
4 = A2/Hong Kong/1/68
5 = A/swine/Wisconsin/15/30
6 = A/equine-1/Prague/56
7 = A/equine-2/Miami/63
8 = A/FPV/Dutch/27
9 = A/turkey/England/63
10 = A/chicken/Germany N/49
11 = A/duck/England/56
12 = A/duck/Czech./56
13 = A/tern/South Africa/61
14 = A/turkey/Mass./65
15 = A/duck/Ukraine/1/63
16 = A/turkey/Ontario/6118/68

Table 6. Avian influenza viruses with neuraminidase subtypes previously identified in viruses isolated from other hosts

Neuraminidase subtype	Reference strain	Former HA group
N1	A/chicken/Brescia/1902 (Hav1N1)	1
	A/chicken/Scotland/59 (Hav5N1)	5
	A/duck/Germany/210/67 (Hav4N1)	4
	A/duck/Germany/1868/68 (Hav6N1)	6
N2	A/turkey/Massachusetts/65 (Hav6N2)	6
	A/turkey/Wisconsin/66 (Hav6N2)	6
Neq1	A/chicken/Germany " N "/49 (Hav2Neq1)	2
	A/FPV/Dutch/27 (Hav1Neq1)	1
Neq2	turkey/Canada/63 (Hav6Neq2)	6
	quail/Italy/1117/65 (Hav2Neq2)	2
	duck/Ukraine/1/63 (Hav7Neq2)	7

agglutinin and neuraminidases be characterized independently. Sera containing antibodies to both of these virus-coded envelope components are inadequate for this purpose because antibodies to one component may interfere with the accurate characterization of the other, presumably on account of steric effects at the virus surface (Schulman & Kilbourne, 1969). As far as is technically possible, the use of monospecific sera against isolated haemagglutinin and neuraminidase antigens derived from appropriate reference strains should be used. The results of studies with such sera form the basis of the division of the haemagglutinin and neuraminidase antigens into subtypes.

Characterization of the haemagglutinin antigen

The haemagglutinin antigens are divided into subtypes based on the results of haemagglutination-inhibition tests (WHO Expert Committee on Respiratory Virus Diseases, 1959) using monospecific sera against the haemagglutinins derived from designated reference strains. The immunoprecipitin test with monospecific sera may be used whenever possible to supplement the results of haemagglutination inhibition tests. Immunoprecipitin tests (Schild, 1970) are broadly reactive and reveal common reactions among strains within a given subtype that may show only minor relationships in haemagglutination inhibition tests.

Characterization of the neuraminidase antigen

The neuraminidase antigens should be divided into subtypes on the basis of the results of neuraminidase inhibition tests (Webster & Pereira, 1968). Immunoprecipitin tests with antineuraminidase sera may also be used to identify neuraminidase subtypes (Schild & Pereira, 1969; Schild & Newman, 1969). As is the case with haemagglutinin antigens, the neuraminidase inhibition tests reveal antigenic variations within a given subtype and immunoprecipitin tests are more broadly reactive.

GENERAL COMMENTS

The procedures described above are proposed as routine tests for the recognition of haemagglutinin and neuraminidase antigen subtypes and minor antigenic variants. However, the tests may not adequately define antigenic differences that may be important for an understanding of epidemiological events or for the formulation of influenza vaccines. Indeed, the epidemiological significance of minor antigenic changes, as measured by any serological procedure now available, is not fully known. The Influenza Programme of the World Health Organization stresses the need for continuing research in this field and urges the application of newer techniques for the serological study of the envelope antigens of influenza viruses.

It is the intention of WHO that the new system of nomenclature should be brought into use on 1 January 1972.

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RÉSUMÉ

UN SYSTÈME RÉVISÉ DE NOMENCLATURE DES VIRUS GRIPPAUX

Le système actuel de nomenclature des virus grippaux, élaboré par deux comités d'experts de l'OMS en 1953 et 1959, était basé sur les caractéristiques de deux antigènes viraux, la ribonucléoprotéine et l'hémagglutinine. Depuis lors, on a identifié un nouvel antigène, la neuraminidase, dont les variations antigéniques sont indépendantes de celles de l'hémagglutinine. Il s'ensuit que toute description correcte d'un virus grippal doit tenir compte des trois antigènes. Dans le système actuel, il était implicitement admis que l'antigène hémagglutinant des virus A était spécifique de toutes les souches isolées chez une espèce animale donnée. Or, depuis quelques années, l'hémagglutinine et la neuraminidase de certains virus grippaux A humains ont été identifiées chez des souches provenant d'hôtes autres que l'homme.

Le nouveau système de classification des virus grippaux, tel qu'il est proposé dans le présent document, conserve l'ancienne notation relative aux virus B et C. En ce qui concerne les virus A, il comporte maintenant des informations sur les trois antigènes et sur les relations antigéniques entre les hémagglutinines et les neuraminidases de virus isolés chez des hôtes différents. Des suggestions sont faites en vue de normaliser également la classification des virus recombinants.

Le document passe succinctement en revue les méthodes d'analyse antigénique et fournit, sous forme de tableaux, des listes de souches de référence pour les différents sous-groupes antigéniques.

L'OMS se propose de mettre le nouveau système de nomenclature en pratique dès le 1er janvier 1972.

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